PATENT- 5102/PCT/US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: ZHANG, JINGWU Z.	EXAMINER: EWOLDT, GERALD R.
APPLICATION NO.: 10/520,296	ART UNIT: 1644
FILED: MARCH 23, 2006	CONF. NO: 2727
FOR: T CELL RECEPTOR CDR3 SEQUENCES AND METHODS FOR DETECTION	

DECLARATION UNDER 37 C.F.R. §1.132

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. David R. Fitzpatrick, declare as follows:

1. I obtained my Ph.D. in Immunology from the University of Saskatchewan in 1989, where I focused on molecular biology, virology immunology and vaccine development. After academic immunology postings in Australia from 1990-1999, I worked for Immunex Corporation in Seattle and then Amgen Inc. after their acquisition of Immunex, ultimately becoming an Acting Director responsible for development of their inflammatory pipeline. I left Amgen in 2006 to start my own consulting firm, Biotech Clarity Consulting LLC, and have been engaged by Opexa Therapeutics as a paid consultant since about March of 2009. A copy of my Curriculum Vitae is attached hereto as Exhibit 1 for the Examiner's reference.

2. I have reviewed the specification for the above-referenced patent application, and I have read and understood the Office Action mailed to Applicants on May 12, 2009. As I understand it, the Examiner is concerned about whether the peptide

sequences described and claimed by Applicants are long enough to generate an anti-idiotypic immune response, and hence would be capable of use in a vaccine.

3. In particular, the Examiner contends that "regarding the vaccines, to function in that capacity would require that the peptides be bound and presented by MHC class II (which would then, presumably activate regulatory T cells). Applicant's own work, Godkins et al. (2001), teaches that the minimum length of the peptide for MHC class II binding is 12 amino acids (see particularly the first sentence of the Abstract). Thus, Applicant's own work teaches that peptides of 4 to 11 amino acids in length cannot function as vaccines." OA, at p. 4. I would respectfully disagree with the Examiner's position regarding minimum peptide length as well as the conclusions drawn from the referenced publication, as I will explain in more detail below.

4. Contrary to the Examiner's suggestion, it is well established in the art that peptides having less than twelve amino acids can generate sufficient B cell and/or T cell responses for antigenic and immunogenic purposes, and in fact the scientific literature is replete with references supporting this proposition. Moreover, in my experience the requisite size threshold is typically lower where, as here, the vaccine is to be administered therapeutically in the face of an already-primed and ongoing immune response, and works by modulating that response. Accordingly, in my opinion, smaller TCR peptides of 6-8 amino acids may readily be used in a vaccine to generate an anti-idiotypic immune response as contemplated and described by the Applicants. I believe the following literature discussion further supports my conclusion.

5. As but one example of a productive B cell response to smaller peptides, LHRH peptides as small as five amino acids were found to be both antigenic and immunogenic, and were successfully used to generate neutralizing antibody responses that modulated fertility in mice. Zeng *et al. Mol Immunol* 44:3724-3731 (2007) (attached hereto as Exhibit 2). Moreover, there are any number of commercially available antibodies recognizing peptides that are less than 12 amino acids in length, *e.g.*, thyrotropin releasing hormone (length = three amino acids), angiotensin II (length = 8 amino acids) (Exemplary data sheets for these antibodies are attached hereto as

Exhibit 3). Indeed, it is worth noting in this regard that the minimum size for antibody recognition can be as low as 1-2 amino acids, as was shown for anti-phospho-tyrosine monoclonal antibodies and anti-dipeptide huMAb such as those described by Kikumoto et al in *Hybridoma* (1995) 14(1):45-50 (copy attached as Exhibit 4).

6. Similarly, there is also a wealth of literature documenting that T cell responses (both CD8+ and CD4+) can be raised against epitopes ranging from 6 to 9 amino acids in length. *See, e.g.* Marttila *et al. Clin. Exp. Immunol.* 104:394-397 (1996) (rubella CD4 epitope) (Exhibit 5);Rajadhyaksha and Thanavala, *Proc. Natl Acad. Sci. USA* 92:1575 (1995) (hepatitis B dual T & B epitope) (Exhibit 6); Cossins *et al. Virology* 195:851 (1993) (flu CD8 epitope) (Exhibit 7); Sheil *et al. Eur. J. Immunol.* 24:2141 (1994) (cytochrome c CD8 epitope) (Exhibit 8); and Yagi *et al. Cancer Res.* 66(20):10136-10144 (2006) (demonstrating elicitation of therapeutic immune response *in vivo* after percutaneous administration in humans) (Exhibit 9). In fact, it is commonly understood that the core region of the peptide is bound by anchor residues within the MHC class II groove, and that these anchor residues are generally at positions 2 and 8-9. Accordingly, a peptide of 7 amino acids would be able to span and be bound by the anchor residues.

7. Moreover, although Godkin et al. state "MHC class II heterodimers bind peptides 12-20 aa in length," they also state that "[t]hese longer peptides <u>bind with a core region</u> of similar length, <u>with</u> the <u>nonbound flanking residues</u> of the peptide extending from the ends of an open groove." <u>Godkin</u>, at Introduction (emphasis added). I would also note that Godkin *et al.* were careful to use peptides having a common core region of <u>nine</u> amino acids in order to demonstrate that the unbound flanking regions modulate T-cell reactivity independently of MHC-peptide binding. Thus, they actually suggested that the core region of such peptides need <u>not</u> be at least 12 amino acids in length in order to be bound to and presented by MHC class II molecules. According to Godkin, then, a peptide may be less than 12 amino acids in length and be bound to and presented by MHC class II.

8. Finally, I would also refer the Examiner to the prior published data from the Applicants themselves, where they demonstrated that both an 8-mer TCR peptide as well as a 15mer TCR peptide were able to generate an anti-idiotypic T cell response, and that both peptides had significant inhibitory effect on the T cell responses to the immunodominant peptide of MBP. *See* Zang *et al.*, *Int'l Immunol.* 15:1073-1080 (2003), attached hereto as Exhibit 10. On the basis of this reference and the more general art referenced discussed above, a skilled artisan would readily recognize that the peptides described and claimed by Applicants are well within the acceptable norm for inducing an appropriate anti-idiotype immune response as presently claimed.

9.. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

David R. Fitzpatrick, Ph.D.

Date NOVEMBER 12 2009